mole, and intra-uterine fetal death. Dinoprost has also been given for the induction of labour but has a higher incidence of adverse effects than dinoprostone, and is no longer routinely recommended; more appropriate treatment is discussed on p.2002.

Dinoprost is usually given intra-amniotically for termination of pregnancy. It has been given intravenously, but with a high incidence of adverse effects. The extra-amniotic route has also been used. Dinoprost is given as the trometamol salt, but doses are described in terms of the base; 1.3 mg of dinoprost trometamol is equivalent to about 1 mg of dinoprost.

For the termination of pregnancy during the second trimester 40 mg of dinoprost is given intra-amniotically by slowly injecting 8 mL of a solution containing 5 mg/mL into the amniotic sac. A further dose of 10 to 40 mg may be given after 24 hours if the termination process has not been established or completed and the membranes are still intact. It should not be given continuously for more than 2 days.

Ileus. Ileus induced by vinca alkaloids in 3 patients with carcinoma of the lung was successfully relieved by the intravenous infusion of dinoprost 300 to 500 nanograms/kg per minute for 2 hours twice daily.[1]

1. Saito H, *et al.* Prostaglandin F in the treatment of vinca alkaloid-induced ileus. *Am J Med* 1993; **95:** 549–51.

Preparations

Proprietary Preparations (details are given in Part 3)
Austral.: Prostin F2 Alpha; ***Cz.:*** Enzaprost F; ***Ger.:*** Minprostin F α; ***Gr.:*** Enzaprost; ***Hong Kong:*** Prostin F2 Alpha; ***Hung.:*** Enzaprost F; ***Irl.:*** Prostin F2†; ***Israel:*** Prostin F2 Alpha; ***NZ:*** Prostin F2 Alpha; ***Pol.:*** Enzaprost; ***Rus.:*** Enzaprost F (Энзапрост Ф); Prostin F2 Alfa (Простин F2-Альфа)†; ***S.Afr.:*** Prostin F2 Alpha.

Dinoprostone *(BAN, USAN, rINN)*

Dinoproston; Dinoprostona; Dinoprostonas; Dinoprostoni; Dinoprostonum; Dinoproszton; PGE_2; Prostaglandin E_2; U-12062. (5*Z*,13*E*)-(8*R*,11*R*,12*R*,15*S*)-11,15-Dihydroxy-9-oxoprosta-5,13-dienoic acid; (*Z*)-7-{(1*R*,2*R*,3*R*)-3-Hydroxy-2-[(*E*)-(3*S*)-3-hydroxyoct-1-enyl]-5-oxocyclopentyl}hept-5-enoic acid.

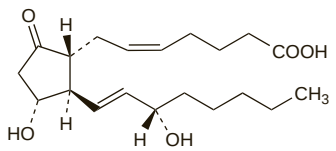
Динопростон

$C_{20}H_{32}O_5$ = 352.5.

CAS — 363-24-6.

ATC — G02AD02.

ATC Vet — QG02AD02.



NOTE. In *Martindale* the term dinoprostone is used for the exogenous substance and prostaglandin E_2 for the endogenous substance.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Dinoprostone). A white or almost white, crystalline powder or colourless crystals. Practically insoluble in water; freely soluble in alcohol; very soluble in methyl alcohol. Store at a temperature not exceeding –15°.

USP 31 (Dinoprostone). A white to off-white, crystalline powder. Freely soluble in alcohol, in acetone, in dichloromethane, in ether, in ethyl acetate, in isopropyl alcohol, in methyl alcohol; soluble in diisopropyl ether and in toluene; practically insoluble in hexanes. Protect from light.

Adverse Effects

The incidence and severity of adverse reactions to dinoprostone are dose-related and also depend to some extent on the route; the intravenous route has been associated with a high incidence of adverse effects. Nausea, vomiting, diarrhoea, and abdominal pain are common by all routes. Back pain and rash can occur. Transient cardiovascular (vasovagal) symptoms have included flushing, shivering, headache, dizziness, and hypotension; there have been rare reports of myocardial infarction and cardiac arrest. Hypertension has also been reported. Convulsions and EEG changes have occurred rarely. Local tissue irritation and erythema, as well as pyrexia and raised white cell count, may follow intravenous doses but generally revert to normal after termination of the infusion. Transient pyrexia and raised white cell count may also occur after intravaginal use. Local infection may follow intra- or extra-amniotic therapy. Excessive uterine activity may occur and there have been occasional reports of uterine rupture after the use of prostaglandins to terminate pregnancy or induce labour; fetal distress and, rarely, fetal death have occurred during induction. Disseminated intravascular coagulation has occurred rarely.

Dinoprostone, although generally acting as a bronchodilator, may cause bronchoconstriction in some individuals. Hypersensitivity reactions have occurred.

Incidence of adverse effects. Adverse effects were evaluated in 626 patients[1] undergoing abortion (usually in the second trimester), using extra-amniotic or intra-amniotic dinoprost or dinoprostone, often with oxytocin. Vomiting occurred in 291, diarrhoea in 28, pyrexia in 34, transient hypotension (fall in systolic blood pressure of at least 20 mmHg) in 25, transient bronchospasm in 2 patients given extra-amniotic dinoprost, and blood loss exceeding 250 mL in 68 (38 lost more than 500 mL). No patients had convulsions even though 8 were being treated for epilepsy. Three patients sustained lacerations to the cervix. Five patients complained of breast soreness or lactation; these symptoms may have been under-reported. Overall 14 patients were re-admitted; 13 because of excessive vaginal bleeding and 1 because of pelvic infection.

A later report describes the cumulative experience in 3313 pregnancies[2] in which dinoprostone gel was used for induction of term labour or cervical ripening. Adverse effects were rare. Vomiting, fever, and diarrhoea occurred in about 0.2% of mothers and were difficult to distinguish from the effects of concurrent drug therapy. Detectable myometrial activity was dose-related and more common after intravaginal than after intracervical use. Myometrial activity was reported in 0.6 to 6% of patients following intravaginal application and hyperstimulation was virtually non-existent at an intracervical dose of 500 micrograms. Fetal effects were negligible in the absence of uterine hyperstimulation.

1. MacKenzie IZ, *et al.* Prostaglandin-induced abortion: assessment of operative complications and early morbidity. *BMJ* 1974; **4:** 683–6.
2. Rayburn WF. Prostaglandin E gel for cervical ripening and induction of labor: a critical analysis. *Am J Obstet Gynecol* 1989; **160:** 529–34.

Effects on the bones. Reversible periosteal reactions of the long bones and bone thickening have occurred in infants receiving long-term therapy with prostaglandins of the E series (see Alprostadil, p.2183). In addition, reversible widening of cranial sutures was reported[1] in 2 neonates given dinoprostone intravenously for 95 and 97 days respectively.

1. Hoevels-Guerich H, *et al*. Widening of cranial sutures after long-term prostaglandin E therapy in two newborn infants. *J Pediatr* 1984; **105:** 72–4.

Effects on the cardiovascular system. Cardiovascular adverse effects are most common after intravenous dinoprostone but may also occur with other routes. Severe cardiovascular disorders reported with the intra-amniotic or intravaginal use of dinoprost or dinoprostone have included: cardiac arrhythmias in 3 patients,[1,2] fatal in 2 of them;[2] hypotension, tachypnoea, and tachycardia in 3 patients[3,4] with associated pyrexias in 2 patients;[3] and fatal myocardial infarction in a patient who had several high-risk factors for ischaemic heart disease.[5]

Severe hypertension occurred in a patient[6] who received dinoprostone by direct myometrial injection and by intravenous infusion concomitantly for postpartum haemorrhage.

Adverse cardiovascular effects have also been reported with other prostaglandins used in gynaecological or obstetric indications (see under Gemeprost, p.2010, and Sulprostone, p.2018).

1. Burt RL, *et al.* Hypokalemia and cardiac arrhythmia associated with prostaglandin-induced abortion. *Obstet Gynecol* 1977; **50:** 45S–46S.
2. Cates W, Jordaan HVF. Sudden collapse and death of women obtaining abortions induced with prostaglandin F . *Am J Obstet Gynecol* 1979; **133:** 398–400.
3. Phelan JP, *et al.* Dramatic pyrexic and cardiovascular response to intravaginal prostaglandin E . *Am J Obstet Gynecol* 1978; **132:** 28–32.
4. Cameron IT, Baird DT. Sudden collapse after intra-amniotic prostaglandin E injection. *Lancet* 1984; **ii:** 1046.
5. Patterson SP, *et al.* A maternal death associated with prostaglandin E . *Obstet Gynecol* 1979; **54:** 123–4.
6. Veber B, *et al.* Severe hypertension during postpartum haemorrhage after i.v. administration of prostaglandin E2. *Br J Anaesth* 1992; **68:** 623–4.

Effects on the fetus. A woman who failed to abort despite receiving carboprost intravaginally 7 weeks after conception gave birth at 34 weeks of gestation to an infant with hydrocephalus and abnormal digits.[1] There have been reports of 2 infants born, without congenital abnormality, to women who continued with the pregnancy after attempted mid-trimester termination using intravaginal gemeprost.[2,3] However, abnormalities including limb deformities, cleft palate, anencephaly, cerebellar atrophy, and heart malformation were reported in a review[4] of 71 cases of pregnancy that were continued after attempted termination using mifepristone either alone or with a prostaglandin. Of the 8 cases of abnormality that were reported, 7 occurred in the group of 10 women who had been given intravaginal gemeprost. A case of cerebellar agenesis has also been described[5] after a failed medical termination using mifepristone and gemeprost. For abnormalities reported after the failed misuse of misoprostol alone for termination of pregnancy, see p.2013.

For reports of adverse effects on the fetus due to hyperstimulation of the uterus during labour, see under Effects on the Uterus, below.

1. Collins FS, Mahoney MJ. Hydrocephalus and abnormal digits after failed first-trimester prostaglandin abortion attempt. *J Pediatr* 1983; **102:** 620–1.
2. Lakasing L, Spencer JAD. Continuation of pregnancy after mid-trimester gemeprost administration. *Br J Obstet Gynaecol* 1999; **106:** 1319–20.
3. Rolland P, Sinha A. Continuation of pregnancy after mid-trimester gemeprost administration. *Br J Obstet Gynaecol* 2000; **107:** 1184.
4. Sitruk-Ware R, *et al.* Fetal malformation and failed medical termination of pregnancy. *Lancet* 1998; **352:** 323.
5. Afadapa FK, Elsapagh K. Isolated one-sided cerebellar agenesis following an attempted medical termination of pregnancy. *J Obstet Gynaecol* 2006; **26:** 581–2.

Effects on the gastrointestinal system. Necrotising enterocolitis has been associated with the use of intravenous[1] or oral[2] dinoprostone, or intravenous alprostadil,[2] in infants with symptomatic congenital heart disease. It has been suggested that induced hypotension and apnoea may be responsible,[1] although others[3] did not support this view, or that pulmonary vasodilatation may produce systemic to pulmonary shunting, rendering the gastrointestinal tract relatively ischaemic.[2]

1. Leung MP, *et al.* Necrotizing enterocolitis in neonates with symptomatic congenital heart disease. *J Pediatr* 1988; **113:** 1044–6.
2. Singh GK, *et al.* Study of low dosage prostaglandin—usages and complications. *Eur Heart J* 1994; **15:** 377–81.
3. Miller MJS, Clark DA. Congenital heart disease and necrotizing enterocolitis. *J Pediatr* 1989; **115:** 335–6.

Effects on the neonate. Aspiration of the undissolved remnants of a dinoprostone vaginal tablet caused neonatal respiratory distress due to mechanical obstruction of the airways; there was no evidence to suggest absorption of dinoprostone from the tablet matrix.[1]

Inadvertent intramuscular injection of carboprost 250 micrograms caused hypertension, bronchospasm, diarrhoea, and hyperthermia in a neonate. There was also an adverse neurological effect that was either a dystonic reaction or seizure activity. The neonate was treated symptomatically and discharged 24 hours later; neurological and developmental examinations were normal at 3 months of age.[2] The authors of this report also learned of 2 other cases that had been reported to the manufacturer, in which neonates given injections of 125 micrograms and 63 micrograms remained asymptomatic.

1. Andersson S, *et al.* Neonatal respiratory distress caused by aspiration of a vaginal tablet containing prostaglandin. *BMJ* 1987; **295:** 25–6.
2. Mrvos R, *et al.* Carboprost exposure in a newborn with recovery. *J Toxicol Clin Toxicol* 1999; **37:** 865–7.

Effects on the nervous system. Convulsions and EEG changes have been occasionally reported during the use of prostaglandins for termination of pregnancy. Convulsions occurred[1] in 5 of 320 women after intra-amniotic dinoprost, but in other large series[2-4] of patients given dinoprost or dinoprostone by various routes no problems occurred despite the inclusion of patients with a history of epilepsy. However, convulsions were reported[5] in 3 of 4 epileptic patients given sulprostone intramuscularly.

1. Lyneham RC, *et al.* Convulsions and electroencephalogram abnormalities after intra-amniotic prostaglandin F . *Lancet* 1973; **ii:** 1003–5.
2. MacKenzie IZ, *et al.* Convulsions and prostaglandin-induced abortion. *Lancet* 1973; **ii:** 1323.
3. Thiery M, *et al.* Prostaglandins and convulsions. *Lancet* 1974; **i:** 218.
4. Fraser IS, Gray C. Electroencephalogram changes after prostaglandin. *Lancet* 1974; **i:** 360.
5. Brandenburg H, *et al.* Convulsions in epileptic women after administration of prostaglandin E derivative. *Lancet* 1990; **336:** 1138.

Effects on the uterus. Use of prostaglandins to induce labour or to terminate pregnancy is associated with an increased risk of hyperstimulation of the uterus. Uterine rupture has occurred with carboprost,[1] dinoprost or dinoprostone,[2-7] gemeprost,[8-10] misoprostol,[11-14] and sulprostone.[15-17] These effects have been reported with parenteral, local, and oral dosage. The risk of rupture and associated complications is increased in grand multiparae[4] and those with uterine scarring from previous caesarean section.[5,7] Studies have reported relative risks of between 6 and 10 times those of spontaneous labour after labour induction with dinoprostone in the latter group.[5,7] In addition to rupture, with the risk of potentially fatal maternal haemorrhage, hyperstimulation has been associated with fetal distress and death,[18-20] and maternal death due to amniotic fluid embolism.[18,21]

1. Vergote I, *et al.* Uterine rupture due to 15-methyl prostaglandin F . *Lancet* 1982; **ii:** 1402.
2. Claman P, *et al.* Uterine rupture with the use of vaginal prostaglandin E for induction of labor. *Am J Obstet Gynecol* 1984; **150:** 889–90.
3. Keller F, Joyce TH. Uterine rupture associated with the use of vaginal prostaglandin E suppositories. *Can Anaesth Soc J* 1984; **31:** 80–2.

4. Larsen JV, *et al*. Uterine hyperstimulation and rupture after induction of labour with prostaglandin E . *S Afr Med J* 1984; **65:** 615–16.
5. Ravasia DJ, *et al*. Uterine rupture during induced trial of labor among women with previous cesarean delivery. *Am J Obstet Gynecol* 2000; **183:** 1176–9.
6. Rabl M, *et al*. A randomized trial of vaginal prostaglandin E for induction of labor: insert vs tablet. *J Reprod Med* 2002; **47:** 115–19.
7. Taylor DR, *et al*. Uterine rupture with the use of PGE vaginal inserts for labor induction in women with previous cesarean sections. *J Reprod Med* 2002; **47:** 549–54.
8. Thavarasah AS, Achanna KS. Uterine rupture with the use of Cervagem (prostaglandin E1) for induction of labour on account of intrauterine death. *Singapore Med J* 1988; **29:** 351–2.
9. Byrne P, Onyekwuluje T. Uterine rupture after termination of pregnancy with gemeprost. *BMJ* 1991; **302:** 852.
10. Vine SJ, *et al*. Transverse posterior cervicoisthmic rupture after gemeprost pessaries for termination. *BMJ* 1992; **305:** 1332.
11. Blanchette HA, *et al*. Comparison of the safety and efficacy of intravaginal misoprostol (prostaglandin E) with those of dinoprostone (prostaglandin E) for cervical ripening and induction of labor in a community hospital. *Am J Obstet Gynecol* 1999; **180:** 1551–9.
12. Mathews JE, *et al*. Uterine rupture in a multiparous woman during labor induction with oral misoprostol. *Int J Gynaecol Obstet* 2000; **68:** 43–4.
13. Khabbaz AY, *et al*. Rupture of an unscarred uterus with misoprostol induction: case report and review of the literature. *J Matern Fetal Med* 2001; **10:** 141–5.
14. Nayki U, *et al*. Uterine rupture during second trimester abortion with misoprostol. *Fetal Diagn Ther* 2005; **20:** 469–71.
15. Larue L, *et al*. Rupture d'un utérus sain lors d'une interruption de grossesse par prostaglandines au deuxième trimestre. *J Gynecol Obstet Biol Reprod (Paris)* 1991; **20:** 269–72.
16. Prasad RNV, Ratnam SS. Uterine rupture after induction of labour for intrauterine death using the prostaglandin E analogue sulprostone. *Aust N Z J Obstet Gynaecol* 1992; **32:** 282–3.
17. de Boer MA, *et al*. Low dose sulprostone for termination of second and third trimester pregnancies. *Eur J Obstet Gynecol Reprod Biol* 2001; **99:** 244–8.
18. Stronge J, *et al*. A neonatal and maternal death following the administration of intravaginal prostaglandin. *J Obstet Gynaecol* 1987; **7:** 271–2.
19. Quinn MA, Murphy AJ. Fetal death following extra-amniotic prostaglandin gel: report of two cases. *Br J Obstet Gynaecol* 1981; **88:** 650–1.
20. Simmons K, Savage W. Neonatal death associated with induction of labour with intravaginal prostaglandin E : case report. *Br J Obstet Gynaecol* 1984; **91:** 598–9.
21. Less A, *et al*. Vaginal prostaglandin E and fatal amniotic fluid embolus. *JAMA* 1990; **263:** 3259–60.

Overdosage. Severe adverse effects associated with intra-amniotic prostaglandins have been attributed to absorption into the systemic circulation of doses higher than would normally be given systemically. Rigors, vomiting, severe abdominal pain, and an intense desire to urinate and defaecate occurred[1] in 3 patients given dinoprostone intra-amniotically for mid-trimester abortion; one patient had peripheral vasoconstriction and a rapid low-volume pulse, with hypotension, and another had peripheral cyanosis. It was suggested[2] that this might have been due to displacement of the needle or cannula outside the amniotic sac. In 2 of the patients prior use of urea may have increased the rate of absorption of prostaglandins from the amniotic cavity. In a further report[3] flushing, severe headache, and nausea immediately after a test dose of dinoprost 2.5 mg was also thought to be due to incorrect positioning of the needle and consequent injection into the systemic circulation; at least part of the dose might have been injected into the peritoneal cavity.[4]

Severe reactions have also been reported with prostaglandins given to abort hydatidiform moles. A 20-year-old woman given 20 mg of dinoprostone by injection into the uterine cavity developed profound hypotension, bradycardia, and rigors, followed by nausea, vomiting, suprapubic pain, an increased pulse rate, pyrexia, and generalised flushing.[5] Since there are no fetal membranes in a molar pregnancy, intra-uterine administration is similar to extra-amniotic administration and the dose used was 100 times higher than the usual extra-amniotic dose.[4] However, in a similar patient[6] 'extra-amniotic' instillation of dinoprostone 200 micrograms was followed immediately by nausea, retching, severe abdominal pain, dizziness, difficulty in breathing and the production of frothy blood-stained sputum, an imperceptible pulse, and hypotension; the dinoprostone had probably been injected directly into the maternal circulation.

1. Ross AH, Whitehouse WL. Adverse reactions to intra-amniotic urea and prostaglandin. *BMJ* 1974; **1:** 642.
2. Craft I, Bowen-Simpkins P. Adverse reactions to intra-amniotic urea and prostaglandin. *BMJ* 1974; **2:** 446.
3. Brown R. Adverse reactions to intra-amniotic prostaglandin. *BMJ* 1974; **2:** 382.
4. Karim SMM. Adverse reactions to intra-amniotic prostaglandin. *BMJ* 1974; **3:** 347.
5. Smith AM. Adverse reactions to intra-amniotic prostaglandin. *BMJ* 1974; **2:** 382–3.
6. McNicol E, Gray H. Adverse reaction to extra-amniotic prostaglandin E . *Br J Obstet Gynaecol* 1977; **84:** 229–30.

Precautions

Dinoprostone should not be given to patients in whom oxytocic drugs are generally contra-indicated (see also Oxytocin, p.2016), because spontaneous labour or vaginal delivery are liable to harm either the mother or the fetus. This includes significant cephalopelvic disproportion or unfavourable presentation of the fetus, placenta praevia, or fetal distress. It should not be used where there is a predisposition to uterine rupture, as in high parity or the presence of a uterine scar from previous caesarean section or major uterine surgery, or in those with a history of pelvic inflammatory disease. Since prostaglandins enhance the effects of oxytocin, use of these drugs together or in sequence should be carefully monitored.

Dinoprostone is contra-indicated in active cardiac, pulmonary, renal, or hepatic disease. It should be used with caution in patients with glaucoma or raised intraocular pressure, a history of asthma or epilepsy, hepatic or renal impairment, or cardiovascular disease.

In the induction of labour cephalopelvic relationships should be carefully evaluated before use. During use uterine activity, fetal status, and the progress of cervical dilatation should be carefully monitored to detect adverse responses, such as hypertonus, sustained uterine contractions, or fetal distress. In patients with a history of hypertonic uterine contractility or tetanic uterine contractions, uterine activity and the state of the fetus should be continuously monitored throughout labour. Where high-tone myometrial contractions are sustained the possibility of uterine rupture should be considered.

Dinoprostone should not be given by the myometrial route, since there is a possible association with cardiac arrest in severely ill patients. The extra-amniotic route should not be used in patients with cervicitis or vaginal infections. Vaginal preparations of dinoprostone should not be used in the induction of labour once the membranes are ruptured. In some countries, intravenous prostaglandins are considered to be contra-indicated in women who smoke.

Dinoprostone should be used with caution in women over 35 years of age, those with complications during pregnancy, such as gestational diabetes, hypertension, or hypothyroidism, and in those past the fortieth week of pregnancy as their condition may further enhance the increased risk of disseminated intravascular coagulation in the immediate postpartum period associated with pharmacologically induced labour.

In the therapeutic termination of pregnancy, fetal damage has been seen in cases of incomplete termination and the appropriate treatment for complete evacuation of the uterus should therefore be instituted whenever termination is unsuccessful or incomplete. Dinoprostone should not be used for termination in patients with pelvic infection, unless adequate treatment has already been started.

Administration. For the hazards of unintentional systemic absorption of prostaglandins after intra-uterine use for the termination of pregnancy and abortion of hydatidiform moles, see Overdosage in Adverse Effects, above.

Interactions

Dinoprostone enhances the effects of oxytocin on the uterus. There is a theoretical risk that prostaglandin synthetase inhibitors, such as aspirin and NSAIDs, might alter the efficacy of dinoprostone.

Uterine stimulants. Marked hypertension, vomiting, and severe dyspnoea occurred after the sequential use of *oxytocin*, *methylergometrine*, and *dinoprost* within the space of 10 minutes to a woman with postpartum haemorrhage.[1]

1. Cohen S, *et al*. Severe systemic reactions following administration of different ureotonic [uterotonic] drugs. *N Y State J Med* 1983; **83:** 1060–1.

Uses and Administration

Dinoprostone is a prostaglandin of the E series (p.2374) with actions on smooth muscle; the endogenous substance is termed prostaglandin E_2 and is rapidly metabolised in the body. It induces contraction of uterine muscle at any stage of pregnancy and is reported to act mainly as a vasodilator and as a bronchodilator. In the UK, dinoprostone is used principally in the induction of labour (p.2002); it may also be used for the termination of pregnancy (p.2004), missed abortion, hydatidiform mole, and intra-uterine fetal death.

Dinoprostone is usually given vaginally. It may also be given intravenously, extra-amniotically, or orally, but the intravenous route has been associated with a high incidence of adverse effects and is generally only used for missed abortion or hydatidiform mole; continuous use for more than 2 days is not recommended.

For the **induction of labour** dinoprostone is used to ripen (soften and dilate) the cervix before the membranes are ruptured and to induce labour at term. The cervical gel used for cervical ripening contains 500 micrograms in 2.5 mL, whereas the vaginal gel used for induction of labour contains 1 or 2 mg in 2.5 mL; the vaginal gel should not be used in the cervical canal. Pessaries are also available for both cervical ripening and labour induction. These are not bioequivalent to the gels and their dosage is different.

To soften and dilate the cervix before induction of labour dinoprostone 500 micrograms is given as *cervical gel*. This dose may be repeated after 6 hours if there was no response to the initial dose; in some cases a third dose may be used to a maximum cumulative dose of 1.5 mg in 24 hours.

For induction of labour the dose as *vaginal gel* is 1 mg (or 2 mg in primigravid patients with unfavourable induction features) followed, if necessary, by a further 1 or 2 mg after 6 hours; a total dose of 3 mg (or 4 mg in unfavourable primigravid patients) should not be exceeded. Alternatively a *vaginal pessary* containing 3 mg may be used and this may be followed, if necessary, by a further 3 mg after 6 to 8 hours; a total dose of 6 mg should not be exceeded.

A *modified-release vaginal pessary* containing 10 mg and delivering about 300 micrograms/hour can be used for cervical ripening and subsequent labour induction. If satisfactory cervical ripening does not occur within 12 or 24 hours, depending on the preparation, then it should be removed.

Dinoprostone may be given *orally* for the induction of labour in an initial dose of 500 micrograms, repeated hourly, and increased if necessary to 1 mg hourly until an adequate response is achieved; single doses of 1.5 mg should not be exceeded. Oral use has, however, generally been replaced by intravaginal dosage since the latter is associated with fewer gastrointestinal adverse effects.

Dinoprostone has been given *intravenously* for the induction of labour but is no longer recommended for routine use by most authorities. A suggested intravenous dosage has been 250 nanograms/minute infused as a solution containing 1.5 micrograms/mL for 30 minutes, the dose being subsequently maintained or increased according to the patient's response; in intrauterine fetal death higher doses may be required and an initial rate of 500 nanograms/minute has been used with increases at intervals of not less than 1 hour.

For the **termination of pregnancy** in the second trimester 1 mL of a solution containing dinoprostone 100 micrograms/mL may be instilled *extra-amniotically* through a suitable Foley catheter, with subsequent doses of 1 or 2 mL given at intervals usually of 2 hours, according to response. Dinoprostone has also been given *intravenously* for the termination of pregnancy and for missed abortion or hydatidiform mole. A solution containing 5 micrograms/mL may be infused at a rate of 2.5 micrograms/minute for 30 minutes, the infusion then being maintained or increased to a rate of 5 micrograms/minute; this rate should be maintained for at least 4 hours before making further increases.

In the USA dinoprostone pessaries are used for the termination of second trimester pregnancy. A dose of 20 mg is given *intravaginally* and repeated every 3 to 5 hours according to response for up to 2 days; a total dose of 240 mg should not be exceeded. Pessaries are also used in the USA in missed abortion, intra-uterine fetal death, and benign hydatidiform mole.

Dinoprostone is used in some centres to maintain the patency of the ductus arteriosus (see below).

Haemorrhagic cystitis. Dinoprostone instilled into the bladder for 4 hours and repeated for 4 days successfully improved severe cyclophosphamide-induced haemorrhagic cystitis (p.702) in a bone marrow transplant recipient.[1] Similar results were obtained in another series of 10 patients.[2]

1. Mohiuddin J, *et al.* Treatment of cyclophosphamide-induced cystitis with prostaglandin E . *Ann Intern Med* 1984; **101:** 142.
2. Laszlo D, *et al.* Prostaglandin E2 bladder instillation for the treatment of hemorrhagic cystitis after allogeneic bone marrow transplantation. *Haematologica* 1995; **80:** 421–5.

Hepatic disorders. See under Alprostadil, p.2184, for reference to the use of prostaglandins, including dinoprostone, in the treatment of viral hepatitis.

Patent ductus arteriosus. Prostaglandins, particularly alprostadil (p.2184) and dinoprostone, may be used to maintain the patency of the ductus arteriosus in infants with congenital heart disease until surgery can be performed to correct the malformation. Treatment for a longer period, especially with oral dinoprostone, may facilitate later surgery by allowing growth of the infants and their pulmonary arteries.

Beneficial responses to long-term use of dinoprostone have been reported.[1,2] Dinoprostone has been given orally in an initial dose of 20 to 25 micrograms/kg hourly, decreasing the frequency of doses after the first week; it was suggested that treatment should be continued for up to 4 weeks initially and a decision then made whether to proceed with surgery or to plan a longer course of treatment to encourage further growth. When gastrointestinal absorption is expected to be poor or when oral treatment is ineffective, dinoprostone has been given by intravenous infusion. The *BNFC* recommends an initial dose of 5 to 10 nanograms/kg per minute increased as necessary, in steps of 5 nanograms/kg per minute, to 20 nanograms/kg per minute; further increases may be needed and doses of up to 100 nanograms/kg per minute have been used, however, these are associated with an increased risk of adverse effects.

1. Silove ED, *et al.* Evaluation of oral and low dose intravenous prostaglandin E in management of ductus dependent congenital heart disease. *Arch Dis Child* 1985; **60:** 1025–30.
2. Thanopoulos BD, *et al.* Prostaglandin E administration in infants with ductus-dependent cyanotic congenital heart disease. *Eur J Pediatr* 1987; **146:** 279–82.

Pemphigus. Erosive oral lesions in 3 patients[1] with pemphigus vulgaris (p.1582), that had previously been refractory to standard corticosteroid therapy, resolved on sucking oral dinoprostone tablets 1.5 to 3 mg daily. Symptoms recurred within weeks of ceasing dinoprostone but could be controlled by courses of 0.5 to 1 mg daily for 1 to 2 weeks, when required. In a group of 10 patients,[2] topical dinoprostone produced similar results in 6 patients, but disease was exacerbated in the others; the dinoprostone was applied twice daily, but details of the dosage form and dose were not reported.

1. Morita H, *et al.* Clinical trial of prostaglandin E on the oral lesions of pemphigus vulgaris. *Br J Dermatol* 1995; **132:** 165–6.
2. Kumaran MS, Kanwar AJ. Efficacy of topical PGE2 in recalcitrant oral lesions of pemphigus vulgaris: a clinical trial. *J Eur Acad Dermatol Venereol* 2006; **20:** 898–9.

Peripheral vascular disease. Various prostaglandins have been used in the treatment of peripheral vascular disease (p.1178), particularly in severe Raynaud's syndrome (see Vasospastic Arterial Disorders, p.1188), but do not constitute mainline therapy.

Postpartum haemorrhage. Dinoprostone and other prostaglandins have been used to control severe postpartum haemorrhage (p.2003) unresponsive to ergometrine and oxytocin.

Beneficial response to continuous intra-uterine irrigation with dinoprostone solution 1.5 micrograms/mL was seen in 22 patients with postpartum haemorrhage unresponsive to other treatment.[1] Postpartum haemorrhage was controlled in another patient using a dinoprostone 3-mg vaginal suppository held against the uterine wall.[2]

1. Peyser MR, Kupfermine MJ. Management of severe postpartum hemorrhage by intrauterine irrigation with prostaglandin E . *Am J Obstet Gynecol* 1990; **162:** 694–6.
2. Markos AR. Prostaglandin E intrauterine suppositories in the treatment of secondary postpartum hemorrhage. *J R Soc Med* 1989; **82:** 504–5.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Prolisina E2; Propess; ***Austral.:*** Cervidil; Prostin E2; ***Austria:*** Prepidil; Propess; Prostin E2; ***Belg.:*** Prepidil; Prostin E2; ***Canad.:*** Cervidil; Prepidil; Prostin E2; ***Cz.:*** Prepidil; Propess; Prostin E2; ***Denm.:*** Minprostin; ***Fin.:*** Minprostin; Propess; ***Fr.:*** Prepidil; Propess; Prostine E ; ***Ger.:*** Minprostin E ; Prepidil; Propess; ***Gr.:*** Minprostin; Propess; Prostin E2; ***Hong Kong:*** Prostin E2; ***Hung.:*** Prepidil; Propess†; Prostin E2; ***India:*** Cerviprime; Primiprost; ***Indon.:*** Prostin E2; ***Irl.:*** Prostin E2; ***Israel:*** Prepidil; Propess; Prostin E2; ***Ital.:*** Prepidil; Propess; Prostin E2; ***Malaysia:*** Prostin E2; ***Mex.:*** Prepidil; Propess; ***Neth.:*** Prepidil; Propess; Prostin E2; ***Norw.:*** Minprostin; ***NZ:*** Cervidil; Prostin E2; ***Pol.:*** Prepidil; Propess; ***Port.:*** Propess; Prostin E2; ***Rus.:*** Prepidil (Препидил); Prostin E2 (Простин Е2)†; ***S.Afr.:*** Prandin E ; Prepidil; Propess; Prostin E2; ***Singapore:*** Prostin E2; ***Spain:*** Prepidil; Propess; ***Swed.:*** Minprostin; Propess; ***Switz.:*** Prepidil†; Propess; Prostin E2; ***Thai.:*** Prostin E2; ***UK:*** Propess; Prostin E2; ***USA:*** Cervidil; Prepidil; Prostin E2.

Ergometrine Maleate *(BANM, rINNM)*

Ergobasine Maleate; Ergometriinimaleaatti; Ergométrine, maléate d'; Ergometrinhydrogenmaleat; Ergometrini maleas; Ergometrinmaleat; Ergometrin-maleát; Ergometrin-maleinát; Ergometrino maleatas; Ergonovine Bimaleate; Ergonovine Maleate; Ergostetrine Maleate; Ergotocine Maleate; Maleato de ergobasina; Maleato de ergometrina; Maleato de Ergonovina. *N*-[(*S*)-2-Hydroxy-1-methylethyl]-D-lysergamide hydrogen maleate; 9,10-Didehydro-*N*-[(*S*)-2-hydroxy-1-methylethyl]-6-methylergoline-8β-carboxamide hydrogen maleate.

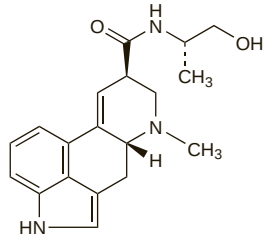
Эргометрина Малеат

$C_{19}H_{23}N_3O_2.C_4H_4O_4$ = 441.5.

CAS — 60-79-7 (ergometrine); 129-51-1 (ergometrine maleate).

ATC — G02AB03.

ATC Vet — QG02AB03.



(ergometrine)

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 6.2 (Ergometrine Maleate). A white or almost white or slightly coloured, crystalline powder. Sparingly soluble in water; slightly soluble in alcohol. A 1% solution in water has a pH of 3.6 to 4.4. Store in airtight glass containers at a temperature of 2° to 8°. Protect from light.

USP 31 (Ergonovine Maleate). A white to greyish-white or faintly yellow, odourless, microcrystalline powder. It darkens with age and on exposure to light. Sparingly soluble in water; slightly soluble in alcohol; insoluble in chloroform and in ether. Store in airtight containers at a temperature not exceeding 8°. Protect from light.

Stability. Deterioration and degradation of ergometrine-containing injections has been seen when exposed to high temperatures in the tropics.[1-4] The mean loss in one study[3] of ergometrine injection under shipment to the tropics was 5.8%, but in some individual samples the loss was more marked: 18 of 80 test samples contained less than 80% of the stated content, and in 3 cases the content was less than 60%. A similar but much less significant pattern was seen with methylergometrine: the content varied from 98.6 to 99.5% of the labelled amount. Tablets of ergometrine and methylergometrine were also shown to be unstable under simulated tropical conditions, with humidity as the main adverse factor.[5]

1. Walker GJA, *et al.* Potency of ergometrine in tropical countries. *Lancet* 1988; **ii:** 393.
2. Abu-Reid IO, *et al.* Stability of drugs in the tropics. *Int Pharm J* 1990; **4:** 6–10.
3. Hogerzeil HV, *et al.* Stability of essential drugs during shipment to the tropics. *BMJ* 1992; **304:** 210–12.
4. Hogerzeil HV, Walker GJ. Instability of (methyl)ergometrine in tropical climates: an overview. *Eur J Obstet Gynecol Reprod Biol* 1996; **69:** 25–9.
5. de Groot ANJA, *et al.* Ergometrine and methylergometrine tablets are not stable under simulated tropical conditions. *J Clin Pharm Ther* 1995; **20:** 109–13.

Adverse Effects and Treatment

Nausea and vomiting, abdominal pain, diarrhoea, headache, dizziness, tinnitus, chest pain, palpitations, bradycardia and other cardiac arrhythmias, coronary artery vasospasm, myocardial infarction, dyspnoea, and pulmonary oedema have been reported after use of ergometrine. Hypertension may occur, particularly after rapid intravenous dosage; hypotension has also been reported. Hypersensitivity reactions, including shock, have occurred. Ergometrine shows less tendency to produce gangrene than ergotamine, but ergotism has been reported and symptoms of acute poisoning are similar (see p.620).

Adverse effects should be treated as for ergotamine, p.620.

Effects on the respiratory system. Bronchospasm has been reported after use of ergometrine.[1] Although studies *in vitro* on *canine* bronchi have suggested a direct action on smooth muscle, this could not be confirmed in studies using human bronchi.

1. Hill H, *et al.* Ergometrine and bronchospasm. *Anaesthesia* 1987; **42:** 1115–16.

Overdosage. Ergometrine maleate has been given accidentally in adult doses to neonates,[1-5] sometimes instead of vitamin K. Symptoms have included peripheral vasoconstriction, encephalopathy, convulsions, respiratory failure, acute renal failure, and temporary lactose intolerance. When given with oxytocin, water intoxication has also been reported.[1] In all of these cases, recovery occurred after intensive symptomatic treatment including assisted ventilation and anticonvulsants. However, deaths have also been recorded.[5] The long-term outcome of ergometrine overdosage has been reported for 6 infants.[5] Their ages at follow-up ranged from 18 months to 5 years; all had normal physical and behavioural development and neurological outcomes.

1. Whitfield MF, Salfield SAW. Accidental administration of Syntometrine in adult dosage to the newborn. *Arch Dis Child* 1980; **55:** 68–70.
2. Pandey SK, Haines CI. Accidental administration of ergometrine to newborn infant. *BMJ* 1982; **285:** 693.
3. Mitchell AA, *et al.* Accidental administration of ergonovine to a newborn. *JAMA* 1983; **250:** 730–1.
4. Donatini B, *et al.* Inadvertent administration of uterotonics to neonates. *Lancet* 1993; **341:** 839–40.
5. Dargaville PA, Campbell NT. Overdose of ergometrine in the newborn infant: acute symptomatology and long-term outcome. *J Paediatr Child Health* 1998; **34:** 83–9.

Precautions

As for Ergotamine Tartrate, p.620. Ergometrine should also be used with caution in patients with veno-atrial shunts or mitral valve stenosis. Ergometrine is contraindicated for the induction of labour or for use during the first stage of labour. If used at the end of the second stage of labour, before delivery of the placenta, there must be expert obstetric supervision. Its use should be avoided in patients with pre-eclampsia, eclampsia, or threatened spontaneous abortion.

Porphyria. Ergometrine maleate has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Interactions

As for Ergotamine Tartrate, p.621. Halothane has been considered to diminish the effects of ergometrine on the uterus.

Sympathomimetics. Use of *dopamine* in a patient treated with ergometrine was associated with subsequent development of gangrene in both hands and feet.[1] In another case,[2] the use of ergometrine with *noradrenaline* resulted in cyanosis of the hands and necrosis in some of the fingers.

1. Buchanan N, *et al.* Symmetrical gangrene of the extremities associated with the use of dopamine subsequent to ergometrine administration. *Intensive Care Med* 1977; **3:** 55–6.
2. Chuang S-S. Finger ischemia secondary to the synergistic agonist effect of norepinephrine and ergonovine and in a burn patient. *Burns* 2003; **29:** 92–4.

Pharmacokinetics

Ergometrine is reported to be rapidly absorbed after doses by mouth and by intramuscular injection, with onset of uterine contractions in about 5 to 15 minutes and 2 to 7 minutes, respectively. Elimination appears to be principally by hepatic metabolism.

Uses and Administration

Ergometrine has a much more powerful action on the uterus than most other ergot alkaloids, especially on the puerperal uterus. Its main action is the production of intense contractions, which at higher doses are sustained, in contrast to the more physiological rhythmic uterine contractions induced by oxytocin; its action is more prolonged than that of oxytocin.

Ergometrine maleate is used in the active management of the third stage of labour, and to prevent or treat postpartum or postabortal haemorrhage (p.2003) caused by uterine atony; by maintaining uterine contraction and tone, blood vessels in the uterine wall are compressed, and blood flow reduced.

In the **active management of the third stage of labour**, ergometrine maleate and oxytocin are given together under full obstetric supervision. A dose of ergometrine maleate 500 micrograms and oxytocin 5 units is injected intramuscularly after delivery of the anterior shoulder, or, at the latest, immediately after de-